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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/002,211
Filing Date: December 05, 2001
Appellant(s): GOLDENBERG, MILTON D.

Barbara A. McDowell
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on November 26, 2010 appealing from the Office action mailed on February 25, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The appellant's statement of the status of amendments after final rejection contained in the brief in Section III on page 2 is incorrect. Appellant has filed correction containing the correct STATUS OF CLAIMS (see CORRECTION filed on November 26, 2010).

The following is a list of claims that are rejected and pending in the application:
Claims 78-86, 93-108, 114, and 116.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The Summary of the Claimed Subject Matter contained in the Brief is correct.

Clarification of the claimed "B-cell antibody or fragment thereof, which specifically binds to a B-cell" and "antibody specific to a marker associated with a B cell"

The instant specification has not disclosed either the structural elements of the antibody or the fully characterized antigen or marker associated with a B cell either by its structure, formula, chemical name or physical properties or by depositing the protein in a public depository. See Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004). The only disclosed species of a B cell antibody is antibody LL2 directed to normal and malignant-B cells (see last full paragraph on page 12 of the instant specification). However, the specification has not disclosed the antigen specificity of the LL2 antibody.

The specification further discloses that the antibodies can be produced by cell membrane antigens but preferably intracellular antigens (e.g. see lines 10-12 on page 11 of the specification). Furthermore, the specification discloses that the antibody may be cross-reactive with other antigens (e.g. see 2nd full paragraph on page 12 and original claim 7 filed on December 5, 2001).

As such, the "B-cell antibody" or "antibody specific to a marker associated with a B cell" is read as any antibody that binds any or all antigen expressed on or inside a B-cell, wherein the antigen are expressed by a B cell, but not necessarily exclusively expressed by a B cell.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Bussel et al. Blood, vol. 72, no. 1 (1988), pp. 121-127, reference on PTO-892 mailed on July 26, 2007.

Fishwild et al. Nature Biotech. vol. 14, (1996), pp. 845-851, reference on PTO-892 mailed on July 26, 2007.

Grandmont et al. Blood, vol. 101, no. 8 (2003), pp. 3065-3073, reference on PTO-892 mailed on July 26, 2007.

Youinou et al. Autoimmune Reviews vol.5, (2006), pp. 215-221, reference on PTO-892 mailed on August 17, 2006.

Vitetta et al. Science, vol. 313 (2006), pp. 308-309, reference on PTO-892 mailed on July 26, 2007.

EP 0739980	Seed et al.	02-1999.
US 4,861,579	Meyer et al.	08-1989.
US 5,116,944	Sivam et al.	05-1992.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

A) Claims 78-86, 93-108, 114, and 116 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record.

The following written description rejection is set forth herein.

The rejections of record set forth in Sections 4 and 5 on pages 2-7 of the Office Action (mailed on February 25, 2010) are discussed collectively herein.

Claims 78-86, 93-108, 114 and 116 are drawn to a method of ablating normal cell in a subject or a method of treating an immune disease (e.g. independent claim 104) by administering a therapeutically effective amount of a composition comprising a B-cell antibody which specifically binds to a B cell or a marker associated with a B cell. Claims 93, 97-100, and 106-108 further encompass a B-cell antibody that is polyclonal, chimeric or hybrid antibody which binds multiple epitops or antigens.

The specification does not provide adequate written description support for the broad genus of antibodies in the method of ablating normal cell, or a method of treating an immune disease.

The specification discloses that the ablation of certain normal organs and tissues by using a growth factor receptor antibody or a hormone receptor antibody to target end-organ bearing such receptors (e.g. see page 7). The ablation method dose not describe any B-cell antibody or antibody that is specific to a marker associated with a B cell.

The specification has not disclosed "fully characterized antigen or a marker associated with a B-cell, either by its structure, formula, chemical name or physical properties, or by depositing the protein in a public depository" for which the B-cell antibody would bind. See Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004).

Page 9 of the instant specification discloses ablation using organ and tissue targeting antibodies of certain normal cells and tissues as part of another therapeutic strategy in the cytotoxic ablation of the spleen in patients with immune thrombycytopenic purpura (ITP). Again, the ablation methods do not encompass any structural elements of the B-cell antibody or antigen specificity .

Page 12 of the specification discloses antibody and fragment thereof that is specific for B-cells including LL2 directed against normal and malignant B-cells that can be used for treating normal spleen cells in patient with immune disease, lymphoma and other disease. The disclosure of LL2 antibody is not in the context of treatment of ITP as claimed in claim 79. Further, the specification has not disclosed what antigen the LL2 binds.

The claims is directed to a method of ablating normal cells or a method of treating an immune disease in a subject by administering a B cell antibody or fragment thereof which specifically binds to a B cell without encompassing any antigen specificity of the antibody. The claim is generic in the sense that it includes antibodies that specifically binds to B cell surface antigens as well as intracellular proteins inside a B-cell. The single monoclonal antibody LL2 described in the specification is insufficient to represent the genus of the monoclonal antibodies required to practice the claimed ablation method in a subject. There is ample evidence of record that the specificities of anti-B cell antibodies falling within the scope of the genus and the structure of the antigens they bind are expected to vary substantially. For example, Youinou et al. (Autoimmunity Reviews 2006 5:215-221, reference on PTO-892 mailed on August 17, 2006) teach that B-cells express a variety of different cell surface markers depending on the B-cell subsets and locations (e.g. see Table 1 on page 217).

In addition, as evidenced by Seed et al. (EP 0739980, reference of record, see page 3 in particular), a mammalian cell (e.g. B cell) may contain up to 30,000 different mRNA sequences that can be translated to proteins.

Therefore, a mammalian cell such as B-cell can potentially encompass 30,000 protein antigens capable of being used as antigens for producing antibodies. Therefore, the genus of the B-cell antibody are extremely large. Yet the specification fails to provide sufficient written description to show possession of the genus of B-cell antibody for the ablation of normal cells or treating an immune disease including immune thrombocytopenic purpura in a subject. The single species of antibody LL2 without antigen specificity described in the specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed method.

Further, the specification discloses that the antibody may or may not be cross-reactive with other tissues (e.g. see 2nd full paragraph on page 12 and original claim 7 filed on December 5, 2011).

Neither the exemplary embodiments nor the specification's general method appear to describe structural features, in structural terms that are common to the genus. That is, the specification provides neither a representative number of species (B-cell antibody or fragments thereof) to describe the claimed genus, nor a description of structural features that are common to species (B-cell antibody or fragments thereof or fully characterized antigens). The specification provides no structural description of B-cell antibody other than the one specifically exemplified (LL2 antibody). The specification is inadequate to describe the claimed genus of B-cell antibodies. Further, there is no described or art-recognized correlation or relationship between the structure of the invention, the B-cell antibody and its ablation of normal B cell or treatment of immune diseases, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of B-cell antibodies which retain the features essential to the instant invention.

Given that there is insufficient written description in the specification as-filed regarding "B-cell antibody" for reasons discussed above, appellant is not in possession of any B-cell antibody that has additional antigen specificities (e.g. chimeric or hybrid as recited in claims 93,

97-100, and 106-108). Once again, single reference to LL2 antibody is insufficient to provide adequate written description support for "a B-cell antibody" for reasons stated above, let alone written description support for a B cell antibody that binds additional undefined antigens or epitoptes.

As such, appellant is not in possession of the claimed method of ablating normal cells in a subject or method of treating an immune disease by administering a B cell antibody or fragment thereof which specifically binds to a B cells.

B) Claims 102 and 105 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record.

This is a Written Description, New Matter rejection.

The term "B-cell immune disease" recited in claims 102 and 105 is not supported by the original disclosure or claim as filed.

Appellant's amendment, filed February 4, 2008, has introduced the limitation of "B-cell immune disease" but does not direct to support of the term in the instant specification and does not asserts that no new matter has been added.

The specification as filed does not provide sufficient written description of the above-mentioned "limitation". The specification does not provide sufficient support for a method of treating "B-cell immune disease" by administering a B-cell antibody, wherein the "B-cell immune disease" is not recognized as a class of disorders by one of skill in the art. The specification only disclose "an immune disease, lymphoma or other disease" (e.g. see lines 34-35 on page 12 of the instant specification). The instant claims now recite "B-cell immune disease" which is not clearly disclosed in the specification nor recognized by one of skill in the art as a

class of disorder. Therefore, the claims represent a departure from the specification and claims originally filed. Appellant's reliance on generic disclosure (an immune disease) and possibly a single or limited species do not provide sufficient direction and guidance to the features currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

C) Claims 114 and 116 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons of record.

This is a Written Description, New Matter rejection

The term "a marker associated with a B cell" recited in claims 114 and 116 is not supported by the original disclosure or claims as filed.

The term was rejected on the record under the same ground as new matter in the Office Action mailed on August 17, 2006. The rejection was withdrawn after appellant canceled the limitation in the claims (see Office Action mailed on July 26, 2007).

Appellant's amendment, filed on October 15, 2009, directs support to the paragraph next to the last paragraph on page 25 of the specification as follows:

"It will be understood that the invention is not limited to use of known antibodies or markers, but can be practiced with antibodies to any marker produced by or associated with an organ or tissue."

The specification as filed does not provide sufficient written description of the above-mentioned "limitation". The specification does not provide sufficient support for a marker associated with a B cell. The specification only disclose antibody to any markers the instant claims now recite any antibody specific to a marker associated with a B cell, which were not clearly disclosed in the specification without setting forth the relevant identifying characteristics of the marker associated with a B-cell (e.g. structural elements of the antibody or B-cell marker). Therefore, the claims represent a departure from the specification and claims originally filed. Appellant's reliance on generic disclosure of antibodies and possibly a single or limited species do not provide sufficient direction and guidance to the features currently claimed (antibody specific for a marker associated with a B cell). It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

D) Claims 78-86, 93-108, 114, and 116 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record.

The claims are broadly drawn to a method of ablating normal cells in a subject or a method of treating an immune disease (e.g. B-cell immune disease in claim 105 or immune

thrombocytopenic purpura in claim 106) by administering a B-cell antibody or fragment thereof, wherein the antibody specifically binds to a B-cell.

The specification discloses generic methods of making antibody by using whole cell or cell extract as antigen. For example, the specification discloses isolation of cell membrane or intracellular antigens to be used to immunize animals to make antibody (e.g. see page 11 of the instant specification). The specification discloses that the use of intracellular antigen as preferable over cell surface antigen (e.g. see page 11). Thus, the claimed B cell antibody would encompass any or all antibody that binds cell surface as well as intracellular proteins not exclusive to B cells.

The following are the Examples disclosed in the instant specification:

Example 1 discloses imaging pancreatic cells by using monoclonal antibodies raised against Langerhan cells of endocrine pancreas obtained from human autopsy; Example 2 discloses bone marrow ablation using NP-2 monoclonal antibody $F(ab')_2$ with no disclosed antigen specificity; and Examples 3 and 4 disclose endometriosis detection and therapy by using anti-endometrial tissue monoclonal antibody (see Examples 1-4 on pages 23-25 of the instant specification).

None of the Examples teach a method of ablating normal cells in a subject by administering a B-cell antibody that specifically binds to a B-cell. The specification as filed does not provide sufficient guidance, description, and working examples of the claimed method broadly encompassing any immune disease using any B-cell antibody. A person skilled in the art is not enabled to make and use the claimed methods of treating an immune disease using B-cell antibody or fragment thereof and/or B-cell antibody or fragment thereof.

The problem here is that the specification fails to disclose the structure of the antibody or fully characterized antigen either by its structure, formula, chemical name or physical properties or by depositing the protein in a public depository. The specification disclosed a single species of the antibody LL2 directed to normal and malignant-B cell without setting forth the antigen specificity of the LL2 antibody. As such, it would take undue experimentation for one of skill in the art to determine which B-cell antibody or antibody specific to a marker associated with a B-cell can be administered to ablate normal cells or to treat an immune disease including a B-cell immune disease or ITP.

The specification provides for a plan or invitation for those skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute the plan; this is not adequate to constitute enablement in that the specification does not enable any person skilled in the art to make and use the invention as it reads on broad classes of immune diseases and B-cell antibodies.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In addition, it is unpredictable whether all of the B-cell antibodies (including antibodies that bind B-cell surface or intracellular proteins as well as antibodies cross-react to common antigens expressed on a B-cell surface and other cell types, e.g. T cells) can be administered alone or conjugated to "therapeutic agent" and/or "a drug" and/or "a cytokine" to treat immune disease as broadly claimed.

For example, Vitetta et al. (Science 2006, 313:308-309) teach that given the complex structure of antibodies, designing therapeutic antibodies can be unpredictable; in the case of anti-CD28 antibody, although preclinical data show that the antibody was safe when administered to two species of monkeys, healthy humans injected with the anti-CD28 antibody suffered immediate and profound side effects (see pages 308-309).

Therefore, even if a person skilled in the art could produce an antibody that binds to a B-cell specifically, it would take undue experimentation to determine which antibody can be administered to ablate normal cells or to treat any or all immune disease including B-cell immune disease or immune thrombocytopenic purpura. One of skill in the art will not know how to practice the claimed method because the instant specification does not provide sufficient enabling description and guidance regarding method of treating an immune disease by administering B-cell antibody or fragment thereof and/or B-cell antibody or fragment thereof that is conjugated to "therapeutic agent" and/or "a drug" and/or "a cytokine" without knowing the characteristics of antibodies, agents, drugs or cytokines.

In conclusion, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

E) Claims 78, 81-86, 102-105, 114, and 116 stand rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (US Patent 4,861,579) (see entire document).

For the record, the instant B-cell is also read as B-lymphocyte disclosed in Meyer et al.

Meyer et al. teach a method of treating immune diseases such as infection, autoimmune disease by administering an anti-B antibody or fragment thereof that suppresses the response of B-lymphocytes (see entire document, particularly 4th full paragraph on column 3 and claims 1-12). Meyer et al. further teach that said antibody can be conjugated with therapeutic agents such

as radioisotopes, toxins, cytotoxic agents (e.g. see first and second full paragraphs on column 2). Given that the prior art antibody recognizes a B-lymphocyte surface marker (e.g. see lines 52-54 on column 2), the prior art antibody reads onto the instant B-cell antibody specifically binds to a B-cell including antibody specific to a marker associated with a B-cell (as recited in instant claims 114 and 116).

Although the reference is silent about the ablation of normal cells, the claim language or limitation of ablating normal cell does not result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given that the prior art method of suppressing B-lymphocyte in a mammal administered the same anti-B cell antibody to the same patient populations as the instant claims, the prior art method would inherently encompass the ablation of normal cells in the subject.

Therefore, the reference teachings anticipate the claimed invention.

F) Claims 78, 79, 81, 93, 96, 102-107, 114, and 116 stand rejected under 35 U.S.C. 102(b) as being anticipated by Bussel et al. (Blood 1988, 72; 1:121-127) as evidenced by de Grandmont et al. (Blood 2003 101;8:3065-3073).

Bussel et al. teach a method of treating immune thrombocytopenic purpura by administering intravenous immunoglobulins (IVIG) (see entire document, particularly first full paragraph on the right column on page 121).

As evidenced by de Grandmont et al, IVIGs are IgG solutions prepared from pooled plasma of healthy human donors and contain antibodies reacting against a large repertoire of antigens, including those on B lymphocytes, e.g. CD40 (see entire document, particularly lines 1-4 on first paragraph in the right column on page 3065). The method of treating immune thrombocytopenic purpura by administering IVIG taught by Bussel et al. would inherently encompass B-cell antibodies including intact antibody.

Further, although the reference is silent about B-cell antibody or antibody specific for a marker associated with a B cell, evidentiary reference Grandmont et al. show that IVIG does bind epitopes (e.g. CD40) on B-cell. Since the Office does not have a laboratory to test the referenced IVIG, it is appellant's burden to show that the referenced IVIG does not contain B-cell antibodies or antibody specific to a marker associated with a B cell. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). Furthermore, it does not appear that the claim limitation of ablating normal cells results in a manipulative difference in the methods steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d1508 (CAFC2001). It is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable.

Therefore, the reference teachings anticipate the claimed invention.

G) Claims 78, 80, 93, 95-101, 107, and 108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (US Patent 4,861,579) in view of Sivam et al. (US Patent 5,116,944).

The teachings of Meyer et al. have been discussed, supra.

The reference teachings differ from the claimed invention by not describing Fv, single chain antibody, Fab, Fab', $F(ab')_2$, chimeric antibody, and antibody that is conjugated to cytokine.

However, the advantages of using Fv, Fab, Fab', $F(ab')_2$, chimeric antibody, and antibody that is conjugated to cytokine were well known in the art at the time the invention was made. For example, Sivam et al. teach antibody and its fragments such as Fv, single chain antibody, Fab, Fab', $F(ab')_2$, and chimeric antibody can be conjugated to cytokines to improve characteristic such as serum half-live of cytokines, stability, and receptor mediated uptake for better target delivery (see entire document, particularly lines 9-17 of the 2nd full paragraph on column 5, 1st and 2nd full paragraphs on column 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use antibody and its fragments conjugated to cytokines in a method of treating an immune disease because anti-B cell antibody can be used in methods of treating immune diseases and antibody and its fragments such as Fv, single chain antibody, Fab, Fab', $F(ab')_2$ can be conjugated to cytokines to improve characteristic for enhanced therapeutic effect.

Given the teachings of Meyer et al. regarding method of treating an immune disease using anti-B cell antibody, and the teachings of Sivam et al providing methods of making and using antibody and its fragment conjugated with cytokines, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of practicing the claimed method of treating an immune disease by using anti-B cell antibody and its fragments that are conjugated to cytokines.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

H) Claims 78 and 94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer et al. (US Patent 4,861,579) in view of Fishwild et al. (Nature Biotech. 1996, 14:845-851).

The teachings of Meyer et al. have been discussed, supra.

The reference teachings differ from the claimed invention by not describing a human monoclonal antibody.

However, methods of making human monoclonal antibody and its use in therapy were well known in the art at the time the invention was made. Specifically, Fishwild et al. teach method of making human monoclonal antibodies using transgenic mice carrying human immunoglobulin gene loci (see Experimental protocol on the right column on page 849). Fishwild et al. further teach that human monoclonal antibody is less immunogenic and have longer half-life in human, thus, more efficacious than murine antibody (see entire document, particularly 1st full paragraph in the right column on page 845).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use human monoclonal anti-B cell antibody in a method of treating an immune disease because anti-B cell antibody can be used in methods of treating immune diseases and antibody and human monoclonal antibody is more efficacious in human.

Given the teachings of Meyer et al. regarding method of treating an immune disease using anti-B cell antibody, and the teachings of Fishwild et al. providing methods of making and using human monoclonal antibody, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of practicing the claimed method of treating an immune disease by using human monoclonal anti-B cell antibody.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

a) Response to argument to the rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement against claims 78-86, 93-108, 114, and 116.

Appellant's arguments to rejections under 35 USC 112, written description, with respect to "B-cell antibody" and "chimeric, or hybrid antibody which binds multiple epitopes and antigen" (set forth in Section VIIA and VIIB on pages 4-13 of the Brief) are rebutted collective herein.

Appellant's arguments in conjunction with the Foon and the Dorner declarations under 35 CFR 1.132 have been fully considered but have not been found persuasive.

The Foon declaration asserts that there were numerous CD antigens taught by the prior art at the time the invention was made:

4th and the 5th International Workshops,

Stashenko et al. (J. Immunology, 125(4):1678-1685, 1980) teach anti-B1 antibody wherein the B1 is a B-cell antigen,

Nadler et al. (J. Clin. Invest. 1981, 67:134-140) and Liu et al. (J. Immunol. 1987, 139;10:3521-6) teach anti-CD20 antibody 2H7,

Schmid et al. American J. of Pathology (1991, 139;4:701-707) and Shimoyama et al. Japanese Journal of Clinical Oncology. 1983, 13;3:477-488) teach B-cell antigens by B-cell malignancies,

Press et al. (Blood. 1987. 69;2:584-591) teach anti-CD20 antibody for the treatment of refractory malignant B-cell lymphomas,

Press et al. (J. Clin. Oncology. 1989. 7;8:1027-38) teach anti-CD37 antibody in method of treating non-Hodgkin's lymphoma, and

Foon et al. (Blood, 68(1):1-31, 1987) teach thirty monoclonal antibodies reactive to human B cell and predicted the B-cell antibodies would be useful in treating leukemias and lymphomas.

Further, the Foon declaration asserts specific B-cell antibodies were also disclosed in following patent applications:

WO 8804936 (later matured into US Patents 5,721,108, 6,204,023, 6,652,852, 6,893,625) teaches an anti-CD20 antibody.

US 5,247,069 teaches the use of antibody G28-5 to define the B-cell receptor Bp50.

Thus, appellant argues B-cell antibodies were well known in the art at the time the invention was made. The Foon declaration argues that the genus of the B-cell antibodies share the function of binding B-cell antigen and asserts that the reference Foon et al. teach a list of 30 monoclonal antibodies (to B cell surface antigen) available commercially.

Additionally, Foon asserts that one of skill in the art, upon reading the instant specification, would understand that appellant is in possession of a method of the claimed B-cell antibody to treat immune diseases.

The statements and the multiple references in Foon's declaration were in an attempt to show that the claimed B-cell antibodies were known in the prior art at the time the invention was made and that the generic disclosure of antibody against B-cells is sufficient to demonstrate possession of all the known antibodies recognizing B-cell surface CD molecules taught in the prior art.

This is not found persuasive for following reasons:

Contrary to appellant's reliance on the known antibodies in non-patent literatures and certain patent documents, it is noted that none of the species of the antibodies in the references cited by the Foon declaration are disclosed in the instant specification, nor are they incorporated by reference in the specification as filed.

Regarding the written description requirement for an antibody, it is noted that applicant can claim an antibody by its binding affinity as long as applicant discloses a "fully characterized antige", either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository. See Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004).

The problem here is that the instant specification has not disclosed the structural elements of the antibody or fully characterized antigen or a marker associated with a B-cell by its structure, formula, chemical name or physical properties or by depositing the protein in a public depository. The only species of the antibody disclosed is antibody LL2 directed to normal and malignant-B cells (see last full paragraph on page 12 of the instant specification). However, the specification has not disclosed the antigen specificity of the LL2 antibody.

The purpose of the written description requirement is broader than to merely explain how to "make and use"; the appellant must also convey with reasonable clarity to those skilled in the art that at the time the invention was made, he or she was in possession of the invention.

Contrary to appellant's reliance on known antibodies, it is noted that "the hallmark of written description is disclosure. . . . [T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed and actual 'possession' or reduction to practice outside of the specification is not enough; and a description that merely

renders the invention obvious does not satisfy the requirement." See Ariad Pharms., Inc. v. Eli Lilly &. Co., 560 F.3d 1366 (Fed. Cir. 2009).

In this case, given the lack of disclosure of the structure of the B-cell antibody or antibody specific for a marker associated with a B-cell, or fully characterized antigen, the written description requirement of the claimed method encompassing administering the antibody has not been satisfied.

Further, appellant has not established that the specific antibodies recognizing CD antigens on the surface of a B cell shown in the prior art are commensurate in scope with the scope of the claims for which protection is sought. For example, Knapp et al. teach a variety of CD antigens that are not B cell specific, e.g. CD5 antigen, and are shared by various cells in the immune system such as T cells (e.g. see page 1448 of Knapp et al); however, neither the Foon declaration nor appellant's remark has indicated whether those CD antigens fall within the scope of the genus of the B cell antigen.

The claimed B-cell antibody specifically binds to a B-cell is not read as only those antibodies that bind to antigens restricted to a B-cell surface and that in vivo usage of an antibody is unpredictable.

It is noted that during patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." See MPEP 2111.

Here, the instant specification has not defined the meaning of B-cell antibody but discloses that organ-associated or organ-specific antibody can be produced by immunizing animal host with tumors, organ or tissue extract and that it is preferable to use intracellular as opposed to surface and extracellular antigen (e.g. see lines 6-22 of the 1st full paragraph on page 11 of the instant specification). The specification further discloses that the antibody can be cross-reactive (e.g. see 2nd full paragraph on page 12 and original claim 7 filed on December 5,

2001). Therefore, the claimed B-cell antibody when given broadest reasonable interpretation based upon the instant disclosure would read on any antibodies that bind antigen expressed by a B-cell including the intracellular antigens.

The claims are drawn to a method of ablating normal cells in a subject or a method of treating an immune disease by administering a B-cell antibody that specifically binds to a B-cell. The claims are generic in two ways. First the claims are generic in the sense that they include many species of B-cell antibodies that would bind a variety of antigens on B-cells as well as intracellular antigens encompassed by B-cells. Second, the methods are generic because they include different patient populations.

For example, Youinou et al. (Autoimmunity Reviews 2006 5:215-221, reference on PTO-892 mailed on August 17, 2006) teach that B-cells express a variety of different cell surface markers depending on the B-cell subsets and locations (e.g. see Table 1 on page 217). As such, it is not clear how one of skill in the art could correlate the anti-B-cell antibody to the cell subset and location for the method of ablating normal cell in a subject.

In addition, Seed et al. (EP 0739980, reference of record, see page 3 in particular), a mammalian cell (e.g. B cell) may contain up to 30,000 different mRNA sequences that can be translated to proteins. Therefore, a mammalian cell such as B-cell can potentially encompass 30,000 protein antigens capable of being used as antigens for producing antibodies. Yet the specification fails to provide sufficient guidance and directions regarding which antibody can be selected to ablate normal cells or treat an immune disease including immune thrombocytopenic purpura in a subject.

The reliance on the single disclosed LL2 antibody (without setting forth the antigen specificity) does not support the written description of the entire genus of any "B-cell antibody". There is ample evidence of record that the specificities of anti-B cell antibodies falling within the scope of the genus and the structure of the antigens they bind would be expected to vary substantially. For example, Youinou et al. (Autoimmunity Reviews 2006 5:215-221) teach that

B-cells express a variety of different cell surface markers depending on the B-cell subsets and locations (e.g. see Table 1 on page 217). It has been well known that a mammalian cell may contain up to 30,000 different proteins that can be antigen for making antibody (discussion based upon Seed (EP 0739980). Therefore, antibodies to B-cells would be expected to have greater differences in their activities and the in vivo usage of the antibodies would be highly unpredictable.

Appellant and the Foon declaration are relying upon the following specific disclosure for the written description support of the instant claims (see pages 8-9 of the Brief) and asserts that one of skill in the art would understand that the B-cell antibodies share a common function of binding to B-cell surface antigens.

This is not found persuasive for following reasons:

> "ablation of certain normal organs and tissues for other therapeutic purposes, such as the spleen in patients with immune disease or lymphomas, the bone marrow in patients requiring bone marrow transplantation, or normal cell types involved in pathological processes, such as certain T-lymphocytes in particular immune diseases" (page 7, lines 5-10)"

This paragraph describes ablation of normal organs and tissues such as T-lymphocytes and there is no description of B-cell antibody.

> "Another therapeutic application for such organ- and tissue-targeting antibodies conjugated with a toxic agent is for the ablation of certain normal cells and tissues as part of another therapeutic strategy, such as in bone marrow ablation with antibodies against bone marrow cells of particular stages of development and differentiation, and in the cytotoxic ablation of the spleen in patients with lymphoma or certain immune diseases, such as immune thrombocytopenic purpura, etc." (page 9, lines 2-10)"

This paragraph describes a genus of organ and tissue-targeting antibodies in bone marrow ablation of particular stages of development and differentiation. It describes certain immune

diseases, such as immune thrombocytopenic purpura but not B-cell antibody that specifically binds to a B-cell.

> "Specific examples include antibodies and fragments against bone marrow cells, particularly hematopoietic progenitor cells, pancreatic islet cells, spleen cells, parathyroid cells, uterine endometrium, ovary cells, testicular cells, thymus cells, B-cells, T-cells, Null cells, vascular endothelial cells, bile duct cells, gall bladder cells, prostate cells, hormone receptors such as of FSH, LH, TSH, growth factor receptors, such as of epidermal growth factor, urinary bladder cells, and vas deferens cells" (page 12, lines 12-20)

> "Antibodies that target the spleen well include the LL2 (also known as EPB-2) monoclonal antibody, disclosed in Pawlak-Byczkowska, cancer Research, 49:4568-4577 (1989), which is directed against normal and malignant B cells, and which can be used for treating normal spleen cells in patients with immune diseases, lymphoma, and other diseases" (page 12, lines 30-35)"

These two paragraphs are the only description of B-cell antibody and the single species of LL2 antibody (in the absence of defying the antigen specificity) found in the entire specification but the description is not in the context to B-cell immune disease or immune thrombocytopenic purpura. The description makes no distinction whether the antibody against B-cells encompass only those that binds to B-cell surface antigen as asserted by appellant.

There is insufficient written description of the claimed "B-cell antibody" broadly encompassed by the claimed invention. There is a lack of disclosure of sufficient relevant identifying characteristics coupled with a known or disclosed correlation between function and structure of the broadly diverse antibodies employed in the claimed methods.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (B-cell antibody or fragments thereof) to describe the claimed genus, nor does it provide a description of structural features that are common to species (B-cell antibody or fragments thereof).

The specification provides no structural description of B-cell antibody or fully characterized antigen other than the one specifically exemplified LL2 antibody in the absence of antigen specificity; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed B-cell antibodies are and use them in the claimed method. The disclosure is inadequate in describing the claimed genus of B-cell antibodies. Further, there is no described or art-recognized correlation or relationship between the structure of the invention, the B-cell antibody and it's ablation of normal cell or treatment of immune diseases, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of B-cell antibodies which retain the features essential to the instant invention.

Furthermore, Appellant's post filing date evidence submitted to show that certain B-cell antibodies are effective in treating autoimmune disease has been fully considered but have not been found persuasive because the rejection of record is under 35 U.S.C. 112, first paragraph, written description, not enablement. Appellant was not in possession of the claimed method of treating an immune disease by administering the genus of "B-cell antibody" for reasons stated above.

Moreover, in contrast to appellant's reliance on a method of treating systemic lupus erythematosus or primary Sjögren's syndrome using anti-CD22 antibody taught by Dorner et al. (Arthritis Res. Ther. 2006. 8;3:pages 1-11 (renumbered)) or Steinfeld et al. (Expert Opin. Biol. Ther. 2006. 6;9:943-9) and method of treating rheumatoid arthritis by companies such as Wyeth and Genentech, it is noted that appellant has not provided any nexus between the prior art diseases systemic lupus erythematosus, primary Sjögren's syndrome, and rheumatoid arthritis and the instant specification.

In addition, the species of anti-CD22 antibody and anti-CD20 antibody, which are not disclosed in the instant specification, are not in commensurate with the scope of the claimed genus of B-cell antibody and the species of systemic lupus erythematosus, primary Sjögren's syndrome, and rheumatoid arthritis are not in commensurate with the scope of the claimed genus

of "an immune disease". Moreover, these species of antibody and diseases are not disclosed in the instant specification nor were they incorporated by references by the specification as filed.

In conclusion, appellant has not provided sufficient written description of a B-cell antibody or fragment thereof which specifically binds to a B-cell to ablate normal cells in a subject or to treat autoimmune disease including B-cell immune disease or immune thrombocytopenic purpura broadly encompassed by the claimed invention.

Therefore, appellant's arguments have not been found persuasive.

b) Response to the arguments to the rejection under 35 U.S.C. 112, first paragraph, Written Description, New Matter against claims 102 and 105 with respect to "B-cell immune disease".

Appellant's arguments and in conjunction with the Dorner declaration under 37 CFR 1.132 have been fully considered but have not been found persuasive.

Appellant points support of the "B-cell immune disease" to lines 30-35 on page 12 of the instant specification. The Dorner declaration asserts that at the time the invention was made, one of skill in the art would understant that the term "immune disease", when discussed together with a B-cell antibody, ablation of normal spleen cells and "certain immune disease, such as immune thrombocytopenic purpura", meant B-cell immune disease. The Dorner declaration states that the immune thrombocytopenic purpura is an example of B-cell hematologic abnomalities due to the positively regulated immune system. As such, appellant asserts that the specification shows possession of the methods of treating B-cell immune diseases.

This is not found persuasive for following reasons :

Contrary to appellant's reliance on the disclosure of the genus of immune disease and the disclosure of immune thrombocytopenic purpurab (ITP), it is noted that the term "B-cell immune disease" is not disclosed in the originally filed specification.

Appellant points to line 30-35 on page 12 of the instant specification for the support of the "B-cell immune disease". However, page 12 of the specifcation only discloses "immune disease" not "B-cell immune disease" (see lines 30-35 of page 12 of the specification or see below)

> *"Antibodies that target the spleen well include the LL2 (also known as EPB-2) monoclonal antibody, disclosed in Pawlak-Byczkowska, cancer Research, 49:4568-4577 (1989), which is directed against normal and malignant B-cells, and which can be used for treating normal spleen cells in patients* ***with immune diseases, lymphoma, and other diseases****"*

Further, contrary to appellant's reliance upon the disclosure of immune thrombycytopenic purpura to support the B-cell immune disease, it is noted that the only disclosure of ITP is on lines 9-10 on page 9 of the instant specification (see copy below)

> *"Another therapeutic application for such organ- and tissue-targeting antibodies conjugated with a toxic agent is for the ablation of certain normal cells and tissues as part 5 of another therapeutic strategy, such as in bone marrow ablation with antibodies against bone marrow cells of particular stages of development and differentiation, and in the cytotoxic ablation of the spleen in patients with lymphoma or certain immune diseases, such as immune thrombocytopenic purpura, etc."*

The ITP was not disclosed in the context with a method of treating a B–cell immune disease by administering a B-cell antibody.

The problem here is that the "B-cell immune disease" encompassed by the claimed method was not disclosed in the specification and claims originally filed and there is no evidence to show that it is a class of disease recognized by one of skilled in the art.

Therefore, the claims represent a departure from the specification and claims originally filed. Appellant's reliance on generic disclosure an immune disease such as ITP does not provide sufficient written description support for the features currently claimed (a B-cell immune disease). It is noted that a generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Therefore, appellant's arguments and the Dorner declaration have not been found persuasive.

c) Response to the arguments to the rejection under 35 U.S.C. 112, first paragraph, Written Description, New Matter against claims 114 and 116 with respect to "a marker associated with a B cell".

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant argues that the claimed "marker associated with a B cell" is described in lines 19-20 on page 5, lines 8-9 on page 15, lines 12-16 and lines 30-33 on page 12. Appellant asserts that the disclosure of LL2 monoclonal antibody directed against normal and malignant B-cells is sufficient to show possession of an antibody that is specific to "a marker associated with a B cell". Appellant further argues that post filing date reference Stein et al. (Cancer Immunol Immunother., 1993, 37(5):293-8) teach that LL2 antibody shows binding profile consistent with anti-CD22 antibody. Thus, appellant argues that one of skill in the art could have tested any antibodies to B cell markers, including anti-CD19 antibody (which was not disclosed in the instant specification), using similar experiments taught by Stein et al. As such, appellant asserts the instant specification provides sufficient written description support for the claims.

This is not found persuasive for following reasons:

Contrary to appellant's assertion that pages 5, 12, and 15 provides written support for the claims, there is no disclosure for an antibody specific to a marker associated with a B cell in the specification as filed. For example, lines 19-20 on page 5 disclose "an antibody specific to a marker associated with or produced by bone marrow cells"; lines 8-9 on page 15 discloses an antibody which specifically binds a marker produced or associated with a genus of cell or tissue; lines 12-16 on page 12 disclose antibodies against B-cell, but none of these disclosure relied upon by appellant teach an antibody specific to a marker associated with a B cell or any relevant identifying characteristics of the antibody or fully characterized marker.

The specification does not provide sufficient support for a marker associated with a B cell. The specification only disclose a genus of antibody to any markers while the instant claims now recite any antibody specific to a marker associated with a B cell, which were not clearly disclosed in the specification. Therefore, the claims represent a departure from the specification and claims originally filed. Appellant's reliance on generic disclosure of antibodies and a single species of LL2 antibody (in the absence of antigen specificity for the LL2) do not provide sufficient direction and guidance to the features currently claimed (antibody specific for a marker associated with a B cell). It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05.

Therefore, appellant's arguments have not been found persuasive.

d) Response to the arguments to the rejection under 35 U.S.C. 112, first paragraph, enablement against claims 78-86, 93-108, 114, and 116.

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant argues that the claimed B-cell antibodies would exclude certain antibodies, e.g. anti-HLA-DR antibodies Lym-1 and Lym-2, taught by Meyer et al. [US Patent 4,861,579, see detail discussion in rejection under 35 U.S.C. 102(b) discussed above]. Appellant argues that one of skill in the art would understand that the claimed methods encompass administering B-cell antibodies listed in 4th or 5th Workshops (reference cited by Foon's declaration under 35 CFR 1.132) and would not consider antibodies that binds B cell antigens that expressed in low level such as anti-HLA-DR antibodies (Lym-1 and Lym-2 taught by Meyer et al.). Thus, appellant asserts the claimed methods are enabled since one of skill in the art would know how to choose B-cell antibody.

This is not found persuasive for following reasons:

Contrary to appellant's assertion that one of skill in the art would know how to choose B-cell antibody, it is noted that the term "B-cell antibody" reads on any antibody that binds antigens expressed on or in a B-cell, see Clarification of the claimed "B-cell antibody or fragment thereof, which specifically binds to a B-cell" and "antibody specific to a marker associated with a B cell" in Section 5, above.

It is further noted that during patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification.". The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. See MPEP 2111.

Here, the claimed "B-cell antibody which specifically binds to a B-cell", when given broadest reasonable interpretation consistent with the specification, would read on any antibody that would bind to antigens expressed on a B-cell surface as well as intracellular antigens. For example, the specification discloses isolation of cell membrane or intracellular antigens to be used to immunize animals to make antibody and discloses that the use of intracellular antigen as preferable over cell surface antigen (e.g. see page 11 of the instant specification). In addition,

the term does not limit the claims to antibodies that exclusively bind B cells or antibodies that only binds antigens with high expression level. In fact, the originally filed claims (e.g. see claim 14 filed on December 5, 2001) encompass an antibody having a specific immunoreactivity to targeted cells or tissues of at least 60% and a cross-reactivity to other antigens in less than 35%.

Thus, it would take undue experimentation for one of skill in the art to determine which of B-cell antibody that specifically binds B-cells but also cross react with other antigens can be used in a method of ablating normal cells and/or a method of treating an immune disease. There is insufficient guidance or direction in the specification with respect to how to make and select a B-cell antibody for the claimed methods.

Moreover, appellant admits that not all antibodies that bind to B-cell can be used to treat immune diseases; only those antibodies that bind antigens well expressed on normal B cells would be effective in treating immune diseases (e.g. see paragraphs 5 and 6 on page 11 of the Remarks filed on December 26, 2007). Yet the instant claims recite any B-cell antibody or fragment thereof without considering the level of antigens that is expressed on normal B cells. Thus, one of skill in the art would not be able to make and use the claimed invention of a method of treating immune diseases using any B-cell antibodies.

In view of the lack of predictability of the art to which the invention pertains, methods of ablating normal cells in a subject or method of treating an immune disease including a B-cell immune disease or immune thrombocytopenic purpura with a broad range of structurally diverse "B-cell antibody" to a variety of diverse specificities would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Therefore, appellant's arguments have not been found persuasive.

e) Response to the arguments to rejection under 35 U.S.C. 102(b) against claims 78, 81-86, 102-105, 114, and 116 based upon Meyer et al. (US Patent 4,861,579) (see entire document).

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant argues that Meyer et al. do not teach anti-B-cell antibody used to ablate normal cells. Appellant asserts that the teachings of Meyer et al. are only limited to release the side effect from the treatment of autoimmune diseases using antibody against the B-lymphocytes. Further, appellant asserts that independent claims 78 and 104 recites "thereby to ablate the normal cell" thus, appellant asserts that the instant claims are different from the prior art methods. Furthermore, appellant argues that the examples in Meyer et al. uses Lym-1 and Lym-2 antibody that are anti-HLA-DR antibodies not considered to be B-cell antibodies since HLA-DR antigen is only expressed at low level in normal cells. Therefore, appellant asserts that the prior art does not anticipate the instant invention.

This is not found persuasive for following reasons:

For the record, the B-lymphocyte taught in the prior art is read as the same as a B-cell.

It is noted that during patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification.". The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. See MPEP 2111.

Here, the claimed "B-cell antibody which specifically binds to a B-cell" or "antibody specific to a marker associated with a B cell", when given broadest reasonable interpretation consistent with the specification, would read on any antibody that would bind to antigens

expressed on a B-cell surface as well as intracellular antigens. Further, "a marker associated with a B cell" is interpreted as an antigen associated with a B cell.

In contrast to appellant's reliance on the working examples of the prior art, it is noted that a prior art reference must be considered in its entirety, see MPEP 2141.02.

Further, contrary to appellant's assertion that the prior art does not teach the method of ablating it is noted that the claimed method of ablating normal cell in a subject or method of treating an immune disease encompass a single step of administering a therapeutically effective amount of a composition comprising a B-cell antibody which specifically binds to a B-cell, wherein the antibody is read as any antibody that binds to a B-cell antigen specifically. Meyer et al., when considered in its entirety, teach a method of treating immune diseases such as infection, autoimmune disease by administering a pharmaceutically effective amount of an antibody or fragment thereof to a B-lymphocyte marker, wherein the antibody selectively suppresses the B-lymphocyte (see entire document, particularly lines 52-54 in column 2 and claim 1).

Although the reference is silent about the antibody administered being able to ablate normal cells, it does not mean that the reference anti-B-lymphocyte antibody does not have this property. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

The teaching of record has properly shifted burden to applicant. The assertions of counsel cannot take the place of evidence in the record. Appellant has not provided sufficient objective evidence to show that the prior art antibody would not ablate normal cells in a subject.

Furthermore, appellant has not disagreed that HLA-DR antigen expressed on B-cell surface. But rather, appellant argues that since it is expressed at low level, antibodies specific to HLA-DR are not considered B-cell antibodies.

This is not found persuasive because the "B-cell antibody" is read as any antibody that binds antigen expressed on or in a B-cell (see Summary of the Claimed Subject Matter in Section 5 above). Further, since the instant claims do not specify any degree of binding, the claims read on any measurable binding of an antibody to any or all B-cell antigen.

As such, anti-HLA-DR antibody that specifically binds HLA-DR antigen expressed on a B-cell is a B-cell antibody. HLA-DR is also considered a marker associated with a B-cell since it is expressed on a B cell. Thus, the prior art anti-HLA-DR antibodies would also read on an antibody specific to a marker associated with a B cell.

Given that Meyer et al. recognize that antibodies to malignant B-lymphocytes are often cross-reactive with normal B-lymphocytes (see entire document, particularly lines 59-62 on column 2), the prior art method of administering such antibodies to malignant B-lymphocytes cross-reactive with normal B-lymphocyte would inherently result in ablating normal cells including spleen B cells in a subject. It is reasonable to conclude that the same patient population is being administered with the same active agent of B-cell antibody by the same mode of administration in both the instant claims and the prior art reference.

Although the reference is silent about the ablation of normal cells, the claim language or limitation of ablating normal cell does not result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain

by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Therefore, appellant's arguments have not been found persuasive.

f) Response to the arguments to the rejection under 35 U.S.C. 102(b) against claims 78, 79, 81, 93, 96, 102-107, 114, and 116 based upon Bussel et al. (Blood 1988 72;1:121-127) as evidenced by de Grandmont et al. (Blood 2003 101;8:3065-3073).

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant argues Bussel et al. do not teach intravenous immunoglobulins (IVIG) includes antibodies against B-cell. Appellant asserts that the evidentiary reference Grandmont et al. teach IVIG binds CD40 that expressed on the surface of many different cell types rather than B-cell specific. Therefore, appellant argues Grandmont et al. do not provide evidence to show that IVIG contains B-cell antibodies. Appellant argues that therapeutically active ingredient in IVIG is known to interact with Fc gamma receptors. Appellant asserts Grandmont et al. do not teach the use of B-cell antibodies in treatment of ITP. Further, appellant asserts that even if IVIG contains B-cell antibodies, the amount would not constitute a therapeutically effective amount encompassed in the instant method. As such, appellant argues that the rejection should be withdrawn.

This is not found persuasive for following reasons:

Appellant has not disagreed that the IVIG activates B-cell surface molecule such as CD40 as taught by the evidentiary reference Grandmont et al. but rather, appellant argues that the reference relied upon for rejection Bussel et al. do not teach IVIG includes antibodies against B-cell. Further, appellant argues that CD40 molecule expresses on many cell surface in addition

to mature B-cells and most malignant B-cells. Appellant appears to argue that even if IVIG binds CD40 that expressed on B-cell surface, IVIG is not a B-cell antibody since CD40 is not restricted to B-cell. This is not found persuasive because the claimed "the B-cell antibody" is not read as the antibody that binds antigens only expressed on a B-cell and not on other cell types.

Contrary to appellant's arguments that CD40 is not B-cell specific antigen, it is noted based upon the broadest reasonable interpretation of the claimed B-cell antibody or antibody specific for a marker associated with a B cell, the prior art IVIG having binding specificity to B-cell epitopes including CD40 would read onto the instant antibody (see Summary of the Claimed Subject Matter in Section 5 above).

The problem here is that the claimed methods are broadly drawn to a single step of administering a genus of B-cell antibody which specifically binds to a B-cell that read on any antibody that would bind to antigens expressed on a B-cell surface including CD40 which is a B-cell surface molecule taught by Knapp et al. [see page 1449 of Knapp et al. Blood, 1989 74;4;1448-1450, reference relied upon by the Foon declaration under 37 CFR 1.132(b) or see page 78 of the Foon declaration filed 11/30/2007). Therefore, IVIG that binds B-cells would read onto a "B-cell antibody" currently claimed.

Further, contrary to appellant's assertion that the IVIG is not administered in "a therapeutically effective amount", it is noted that the claimed therapeutically effective amount does not define parameter that would exclude the IVIG amount being administered by the prior art. Here, Bussel et al. expressly teach repeated infusion of IVIG at 800 to 1000 mg/kg (e.g. see Abstract). Appellant has not provide objective evidence to show that the prior art's administration of the IVIG is not a therapeutically effective amount that would ablate normal cells in the patients.

Furthermore, once again, in contrast to appellant's reliance on the mechanism of action of IVIG, it is noted that the mechanism of action disclosed by the prior art does not preclude that

the methods and compositions of the prior art IVIG inherently having the properties of B-cell antibody recited in the claims because compositions comprising the same type of B-cell antibodies are administered to the same patients suffering from ITP to treat the same type of autoimmune disease.

Therefore, appellant's arguments have not been found persuasive.

g) Response to the arguments to the rejection under 35 U.S.C. 103(a) against claims 78, 80, 93, 95-101, 107, and 108 based upon Meyer et al. (US Patent 4,861,579) in view of Sivam et al. (US Patent 5,116,944).

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant's arguments and the Examiner's rebuttal regarding the teachings of Meyer et al. are essentially the same as discussed, supra.

Appellant further argues that Sivam et al. only teach antibody fragments and conjugates. Thus, appellant asserts that Sivam et al. fail to overcome the deficiency of Meyer et al., thus, the rejection should be withdrawn.

This is not found persuasive for following reasons:

In response to appellant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Furthermore, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

Here, given the teachings of Meyer et al. regarding method of treating an immune disease using anti-B cell antibody, and the teachings of Sivam et al providing methods of making and using antibody and its fragment conjugated with cytokines, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of practicing the claimed method of treating an immune disease by using anti-B cell antibody and its fragments that are conjugated to cytokines.

h) Response to the arguments to the rejection under 35 U.S.C. 103(a) against claims 78 and 94 based upon Meyer et al. (US Patent 4,861,579) in view of Fishwild et al. (Nature Biotech. 1996, 14:845-851).

Appellant's arguments have been fully considered but have not been found persuasive.

Appellant's arguments and the Examiner's rebuttal regarding the teachings of Meyer et al. are essentially the same as discussed, supra.

Appellant further argues that Fishwild et al. fails to overcome Meyer's failure regarding the treatment of an immune disease with a B-cell antibody. Thus, appellant argues the rejection should be withdrawn.

This is not found persuasive for following reasons:

In response to appellant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Furthermore, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

In this case, given the teachings of Meyer et al. regarding method of treating an immune disease using anti-B cell antibody, and the teachings of Fishwild et al. providing methods of making and using human monoclonal antibody, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of practicing the claimed method of treating an immune disease by using human monoclonal anti-B cell antibody.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Chun Dahle/

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/Ram R. Shukla/

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